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(54) Title: HYPERFORIN DERIVATIVES, THE USE THEREOF AND FORMULATIONS CONTAINING THEM

(57) Abstract: The use of the reduction products of hyperforin and adhyperforin, pharmaceutically acceptable salts or esters thereof, in the pharmaceutical and/or nutritional field, in particular in the treatment of depression and Alzheimer's disease.

HYPERFORIN DERIVATIVES, THE USE THEREOF AND FORMULATIONS CONTAINING THEM

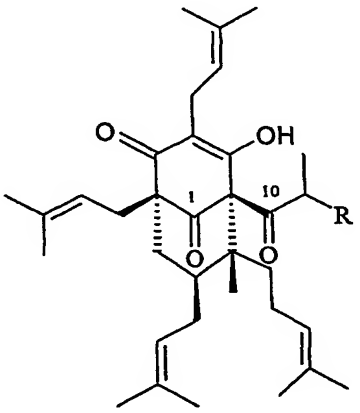
FIELD OF THE INVENTION

The present invention relates to hyperforin and adhyperforin derivatives and the use thereof in the pharmaceutical and/or nutritional field, in particular in the treatment of depression and Alzheimer's disease.

TECHNOLOGICAL BACKGROUND

Flowering tops of *Hypericum perforatum* contain a number of classes of structurally different substances that act directly or indirectly on the central nervous system. The mechanisms of action of these compounds are different and comprise anti-MAO action (Suzuki OR. et al. Planta Med., 272-4, 1984), action on serotonin release and re-uptake (Muller W. E. et al Pharmacopsychiatry, 30, 102-107, 1997) and benzodiazepine-like activity (Coot J.M. Pharmacopsychiatry 30,108-112, 1997).

Hyperforin, a floroglucin derivative, is one of the main components of the lipophilic fraction of *Hypericum perforatum* flowering tops; said fraction also contains adhyperforin, a hyperforin higher homologue, although in lower concentration (Erdelmeier C.A.J., Pharmacopsychiatry, 31, 2-6, 1998).

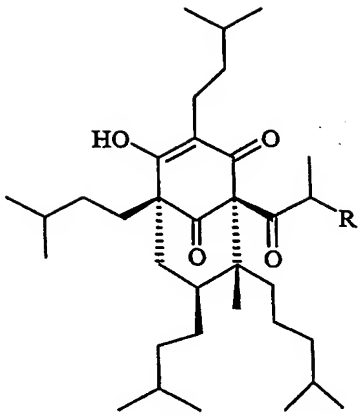


hyperforin: R = CH_3
adhyperforin: R = CH_2CH_3

Hyperforin has recently been the object of numerous studies that establish its important role as an antidepressant (Pharmacopsychiatry, 31 Suppl.1, 1-60. 1998). Furthermore, it is recognized that the extracts of *Hypericum perforatum* can be used for the prophylaxis and treatment of neurodegenerative diseases, *inter alia* Alzheimer's disease (WO/9940905, WO0057707). In particular, hyperforin and adhyperforin salts with inorganic cations or ammonium salts were described for this purpose (WO9941220).

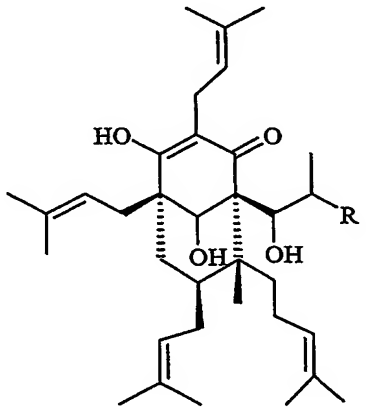
It is known from literature that hyperforin is poorly stable in the usual extraction and storage conditions; according to WO 97/13489, the hyperforin content in a St. John's Wort water-alcoholic extract falls already after a few weeks. WO 97/13489 further recites that, in order to obtain hyperforin stable extracts, antioxidants should be present during the whole work up (extraction, purification and storage). It is therefore evident that the high instability of hyperforin makes the preparation of hyperforin pharmaceutical formulations quite difficult. In order to obviate to said drawback, compounds more stable than hyperforin, such as the salts disclosed in WO 99/41220 and the hydroxy-functionalized derivatives (WO 99/64388) cited above, have recently been prepared.

It is moreover known (Bystrov et al., Bioorg. Khim, 1978) that hyperforin and adhyperforin can be transformed into the corresponding octahydroderivatives, octahydrohyperforin (**Ia**) and octahydroadhyperforin (**Ib**), by catalytic reduction of the isoprene side chains



(Ia: R = CH_3
Ib: R = CH_2CH_3)

or into the corresponding tetrahydroderivatives, tetrahydrohyperforin (**Ic**) and tetrahydroadhyperforin (**Id**), by reduction of the keto groups at the 1- and 10- positions to hydroxy groups with metal hydrides.



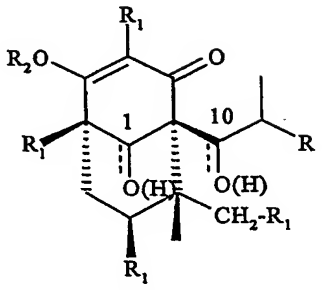
(Ic: R = CH_3
Id: R = CH_2CH_3)

DETAILED DISCLOSURE OF THE INVENTION

It has now been found that hyperforin and adhyperforin derivatives obtainable by reduction of all double bonds of the isoprene chains and/or by reduction of the keto groups at the 1- and 10- positions to hydroxy groups not only have high stability, but also possess antidepressant, anxiolytic and anti-neurodegenerative activities surprisingly higher than hyperforin and adhyperforin.

Object of the present invention is therefore the use of hyperforin and

adhyperforin derivatives of formula (**I**)



(I)

in which R is methyl or ethyl, R_2 is hydrogen, a pharmaceutically acceptable inorganic or organic base cation or a straight or branched C_2-C_5 acyl residue, and in which, alternatively:

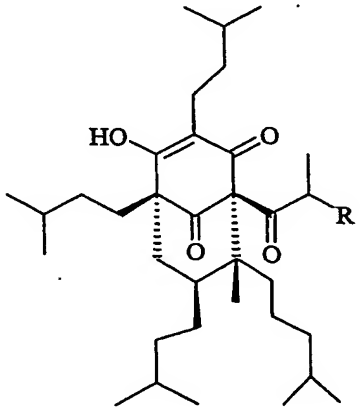
a) R_1 is 3-methyl-but-1-yl and oxo groups are present at the 1- and 10- positions;

b) R_1 is 3-methyl-2-buten-1-yl and hydroxy groups are present at the 1- and 10-positions;

c) R_1 is 3-methyl-but-1-yl and hydroxy groups are present at the 1- and 10-positions.

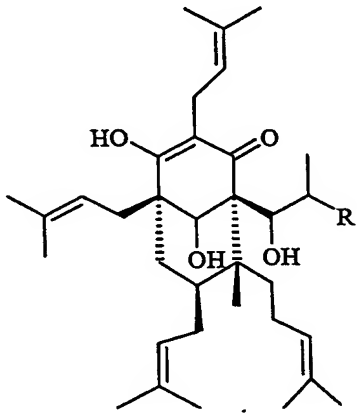
for the preparation of medicaments, in particular for the preparation of medicaments for the treatment of depression and Alzheimer's disease.

Preferred compounds of formula (**I**) as defined at a) are those in which R_2 is hydrogen, in the following defined octahydrohyperforin (**Ia**) and octahydroadhyperforin (**Ib**):



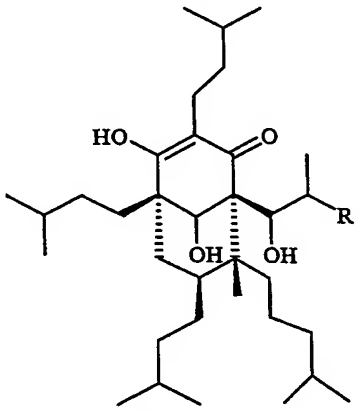
(Ia: R = CH_3
Ib: R = CH_2CH_3)

Preferred compounds of formula (**I**) as defined at b) are those in which R_2 is hydrogen (in the following defined tetrahydrohyperforin **Ic** and tetrahydroadhyperforin **Id**), tetrahydrohyperforin (**Ic**) being most preferred:



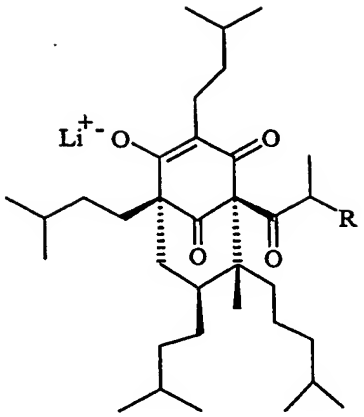
(Ic: R = CH_3
Id: R = CH_2CH_3)

Preferred compounds of formula (**I**) as defined at c) are those in which R2 is hydrogen (in the following defined dodecahydrohyperforin **Ie** and dodecahydroadhyperforin **If**), dodecahydrohyperforin (**Ie**):



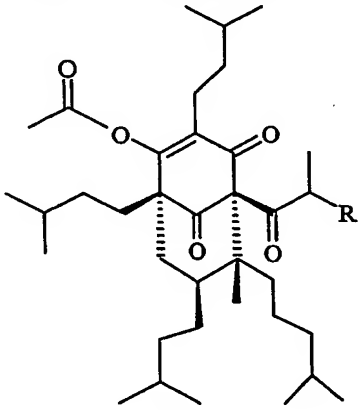
(Ie): R = CH_3
(If): R = CH_2CH_3

Further preferred compounds of formula (**I**) as defined at a) are those in which R_2 is lithium (octahydrohyperforin lithium salt **Ig** and octahydroadhyperforin lithium salt **Ih**), octahydrohyperforin lithium salt (**Ig**) tetrahydrohyperforin (**Ic**) being most preferred:



(Ig: R = CH_3
Ih: R = CH_2CH_3)

Further preferred compounds of formula (**I**) as defined at a) are those in which R_2 is acetyl (acetyloctahydrohyperforin **Ii** and acetyloctahydroadhyperforin **Il**), acetyloctahydrohyperforin (**Ii**) tetrahydrohyperforin (**Ic**) being most preferred:



(Ii: R = CH_3
Il: R = CH_2CH_3)

Dodecahydrohyperforin (**Ie**), dodecahydroadhyperforin (**If**), acetyloctahydrohyperforin (**Ii**) and acetyloctahydroadhyperforin (**Il**) are novel compounds and are also part of the present invention.

The compounds of formula (**Ia**) and (**Ib**) are obtained through reduction of the isoprene side chains by catalytic hydrogenation, using for example palladium on charcoal or Nickel/Raney.

The compounds of formula (**Ic**) and (**Id**) are obtained by reduction of

the keto groups at the 1- and 10- positions with hydrides, selected for example from $NaBH_4$, Redal®, Vitride®, $LiAlH_4$.

The compounds of formula (**Ie**) and (**If**) are obtained by reducing first the isoprene side chains and then the keto groups at the 1- and 10- positions according to what described above.

Compounds of formula (**I**) in which R_2 is an inorganic or organic base cation or an acyl residue, can be prepared from compounds of formula (**I**) in which R_2 is hydrogen by salification or esterification with conventional methods.

The process for the preparation of the compounds of the invention starting from the flowering tops of *Hypericum perforatum* can be summarized as follows:

The flowering tops of *Hypericum perforatum* can be extracted with alcohols or aliphatic ketones, either pure or in a mixture thereof with water or with gas in supercritical conditions; the resulting extract is partitioned between n-hexane and aqueous solutions of aliphatic alcohols. The hexane solution is extracted with alkaline methanol to extract hyperforin and adhyperforin. The methanolic solution is acidified, then treated with a weakly basic ion exchange resin, which selectively retains hyperforin and adhyperforin. The resin is eluted with acidic methanol and the eluate is concentrated to small volume, then diluted with water and back-extracted with n-hexane. The hexane solution is concentrated to small volume and the resulting concentrate is ready for derivatization. The residue is taken up in chlorinated solvents and the suitable reactive is added thereto, according to the procedures reported in the examples.

The compounds of the invention have shown antidepressant effect, which was evaluated in the rat by the forced swimming test, evaluating the parameters: struggling, floating and swimming according to what described by

Cervo et al. in Neuropharmacology, 26, 14969-72, 1987. The compounds were administered in 3 doses: 30 minutes after the pre-test, 5 hours and 30 minutes before the test. The results reported in the table below prove that the compounds of the invention are more active than parent hyperforin.

Treatment	mg/Kg	Struggling (sec.)	Floating (sec.)	Swimming (sec.)
Carrier		7.0 ± 2.4	174.5 ± 15.9	118.5 ± 15.8
Octahydrohyperforin lithium salt	6.25	63.1 ±5.8	59.5 ± 11.3	177.4 ± 14.9
Tetrahydrohyperforin	6.25	51.4 ± 4.1	68.4 ± 7.6	193.4 ± 13.2
Dodecahydrohyperforin	6.25	62.13 ± 5.1	55.1 ± 6.2	169.5 ± 10.1
Acetyloctahydrohyperforin	6.25	73.9 ± 5.9	68.4 ± 5.7	171.9 ± 11.4
Hyperforin	6.25	30.4 ± 4.6	60.4 ± 7.3	99.3 ± 10.6
Desipramin	10	148.3 ± 12.6	53.0 ± 9.2	98.8 ± 7.9

The compounds of the invention also proved particularly active against Alzheimer's disease, due to their ability to increase APPs, the soluble, harmless form of Alzheimer Precursor Protein (APP). It is in fact known that proteolytic cleavage of Alzheimer Precursor Protein (APP) is mediated both by β- and γ-secretase, inducing an increased production of amyloid peptide Ab1-42 (which also plays a central role in the appearance of Alzheimer's disease), and α-secretase, giving raise to soluble APPs which have no pathogenic activity (Eslr W.P., Wolfe M.S., Science, 293,1449-54, 2001).

The effect of the compounds of the invention on the release of APPs produced by α-secretase was evaluated in the culture medium of a neuroblastoma cell line (SH-SY5Y) according to the procedure described by Galbete J.L. et al. in Biochem J. 348,307-313,2000.

The results reported in the following table show that the tested

compounds activate α-secretase – mediated APP metabolism, inducing an increase in APPs secreted in the culture medium:

	APPs %
Controls	100
10 μM Hyperforin	296
10 μM Octahydrohyperforin Lithium Salt	1383
10 μM Tetrahydrohyperforin	926
10 μM Dodecahydrohyperforin	879
10 μM Acetyloctahydrohyperforin	954

The compounds of the invention can be formulated according to conventional techniques, for example according to what described in Remington's Pharmaceutical Sciences Handbook, XVII Ed. Mack Pub., N.Y., U.S.A, in the form of soft-gelatin capsules, hard-gelatin capsules, tablets, suppositories; preferably the extract of the invention is formulated in soft-gelatin capsules or in controlled-release formulations. The dosage ranges from 10 to 100 mg per unit dose in the usual formulations and up to 200 mg in the controlled-release formulations, in this case the suggested dose being 200 mg per dose/daily. Furthermore, the compounds can be administered through the controlled-release transdermal route applying the formulation in the proximal area to the cerebral carotid artery derivations. The dosages of compound in these formulations range from 10 to 100 mg per dose/daily.

The examples reported hereinbelow illustrate the invention in greater detail.

EXAMPLES

Example 1 – Preparation of hyperforin

10 kg of flowering tops of *Hypericum perforatum* and 30 L of methanol are extracted in a 50 L extraction plant and the mass is left to stand at room temperature for 3 hrs; the extraction is repeated 3 more times, then the combined

extracts are concentrated under vacuum to 5 kg and the concentrate is extracted with 3 x 5 L of hexane. The water-methanol solution is discarded, while the hexane one is back-extracted with alkali methanol (KOH) until exhaustion of hyperforin and adhyperforin.

This solution is neutralized and filtered through a weakly basic Amberlite resin, which selectively retains hyperforin and adhyperforin; the retained product is eluted again with methanol acidified with phosphoric acid; the methanolic eluate is concentrated under vacuum at 25°C, the diluted water and back-extracted with n-hexane until exhaustion of of hyperforin.

The combined organic layers are decolourized with 0.3% charcoal, then dried over Na_2SO_4 and concentrated to an oil below 40°C under vacuum. After solidification the oil yelds a wax (0.52 kg) containing approx. 90% of hyperforin.

Example 2 -Preparation of octahydrohyperforin dicyclohexylammonium salt

50 g of hyperforin obtained as described in Example 1 are dissolved in 500 ml of ethyl acetate in the presence of 2 g of 5% palladium on charcoal and hydrogenated until complete hydrogen absorption. The catalyst is filtered off, the solution is concentrated to dryness under vacuum and the residue is dissolved in n-hexane. The solution is added with a stoichiometric amount of dicyclohexylamine, to obtain a sufficiently selective crystallization of the corresponding salt.

62 g of octahydrohyperforin dicyclohexylammonium salt are obtained, having the following spectroscopical characteristics:

^{1}H-NMR (300 MHz $CDCl_3$): δ 3.03 (2H, m, CH-DCHA), 2.55-2.30, 2.10-1.76 (20H, m, CH_2-DCHA), 1.70-1.10 (22H, m, H-4, H-11, CH_2-5, CH_2-15, CH_2-16, CH_2-17, CH_2-21, CH_2-22, CH_2-26, CH_2-27, CH_2-31, CH_2-32), 0.97-0.83 (24H, d, CH_3-19, CH_3-20, CH_3-24, CH_3-25, CH_3-29, CH_3-30, CH_3-34, CH_3-35), 1.19, 1.12 (6H, d, J = 6.5 Hz, CH_3-12, CH_3-13), 0.91 (3H, s, CH_3-14).

^{13}C-NMR (75 MHz $CDCl_3$): δ 213.1, 211.1, 186.3, 183.6 119.0, 82.5, 60.8, 53.5, 47.5, 44.2, 41.3, 41.0, 40.9, 38.2, 38.1, 37.8, 33.8, 31.0, 30.7, 30.0, 29.4, 28.8, 28.3, 27.9, 27.1, 25.4, 25.1, 24.9, 23.5, 23.2, 23.1, 22.9, 22.8, 22.7, 22.5, 13.7. ESIMS *m/z* 567 [M+Na^+] (100), 1111 [2M+Na^+] (91).

Example 3 - Preparation of tetrahydrohyperforin

2 g of hyperforin (M.W. = 536,01) are dissolved in 20 ml of THF under magnetic stirring; the solution is added with $LiAlH_4$ in strong excess (1 g, 0.026 mol, M.W.= 38). The progress of the reaction is monitored by TLC (eluent petroleum ether/EtOAc 9:1). After ten minutes the reaction is completed.

$Na_2S_2O_4 \cdot 10H_2O$ supported on Celite (3:1 by weight) is added to destroy the reactive excess: the reaction is highly exothermic, therefore it should be cooled with ice. Part of the solvent evaporates due to the developed heat. The mixture is filtered through Celite and the filtrate is washed three times with 20 ml of AcOEt. The solution is placed in a 150 ml round-bottom necked flask and the solvent is evaporated off completely.

The resulting mixture is purified by column chromatography, using a 200 ml column packed with 100 ml of silica gel and petroleum ether/EtOAc 95:5 as eluent mixture. Eluate fractions of approx. 20 ml are collected and the content is checked by TLC (petroleum ether/EtOAc 9:1). The more abundant product (1.5 g), crystallized from methanol has the following spectroscopical properties:

^{1}H-NMR (300 MHz $CDCl_3$): δ 5.11 (1H, m, H-22), 5.00 (3H, m, H-17, H-27, H-32), 3.11 (1H, dd, J = 14.0, 7.4 Hz, CH_2-26), 2.92 (1H, dd, J = 14.0, 7.0 Hz, CH_2-26), 2.50-1.35 (12H, m, H-4, H-11, CH_2-5, CH_2-15, CH_2-16, CH_2-21, CH_2-31), 1.80-1.52 (24H, s, CH_3-19, CH_3-20, CH_3-24, CH_3-25, CH_3-29, CH_3-30, CH_3-34, CH_3-35), 1.19-0.95 (9H, d, CH_3-12, CH_3-13, CH_3-14).

^{13}C-NMR (75 MHz $CDCl_3$): δ 200.5, 174.3, 134.1, 132.6, 131.2 130.6,

125.8, 123.9, 122.6, 120.5, 119.4, 79.2, 73.1, 39.6, 37.2, 30.5, 32.8, 31.3, 30.2, 26.1, 26.0, 25.8, 23.5, 23.1, 21.9, 20.0, 18.3, 18.1, 17.8, 15.6.

ESIMS *m/z* 1103 [2M+Na^+] (100), 541 [M+H^+] (25), 563 [M+Na^+] (12).

Example 4 - Preparation of octahydroadhyperforin lithium salt

15 g of octahydrohyperforin dicyclohexylammonium salt are eluted on an acidic resin (Dowex 50X8, 300 g) with 600 ml of methanol. 11.01 g of octahydrohyperforin are obtained, which are added with 0.8745 g of LiOH monohydrate dissolved in water. The mixture is evaporated to dryness to obtain 11.41 g of lithium salt having the following spectroscopical characteristics:

^{1}H-NMR (300 MHz $CDCl_3$): δ 1.93-1.00 (22H, m, H-4, H-11, CH_2-5, CH_2-15, CH_2-16, CH_2-17, CH_2-21, CH_2-22, CH_2-26, CH_2-27, CH_2-31, CH_2-32), 1.00-0.80 (24H, d, CH_3-19, CH_3-20, CH_3-24, CH_3-25, CH_3-29, CH_3-30, CH_3-34, CH_3-35), 1.20, 1.06 (6H, d, J = 6.3 Hz, CH_3-12, CH_3-13), 0.91 (3H, s, CH_3-14).

^{13}C-NMR (75 MHz $CDCl_3$): δ 211.4, 191.3, 184.6, 82.7, 61.5, 51.3, 47.7, 41.5, 40.5, 38.2, 37.9, 37.7, 33.9, 30.5, 29.6, 28.7, 28.3, 28.1, 27.1, 23.3, 23.1, 23.0, 22.8, 22.7, 22.4, 22.0, 14.0.

ESIMS *m/z* 551 [M+H^+] (100), 557 [M+Li^+] (40), 1102 [2M+H^+] (71), 1108 [M+Li^+] (75).

Example 5 - Preparation of dodecahydrohyperforin.

1.72 g of dicyclohexylammonium octahydrohyperforinate (M.W. = 716; 2,41 mmol) are dissolved in 20 ml of THF, under magnetic stirring; the solution is added with a strong excess (3.5 g) of $LiAlH_4$ (M.W.= 38; 0.092 mol). The progress of the reaction is monitored by TLC (eluent petroleum ether/EtOAc 9:1). After ten minutes the reaction is completed.

The reactive excess is destroyed as described in example 5. The mixture is filtered and the residue is thoroughly washed with ethyl acetate. The

solution is evaporated to dryness, the reaction crude is dissolved in 15 ml of petroleum ether/ethyl ether 3:1 and the solution is placed in a 150 ml separatory funnel. The organic phase is washed three times with 2N sulfuric acid and subsequently with brine. The aqueous phase is discarded, the organic one is dried over Na_2SO_4 and concentrated to dryness. The resulting product is purified by column chromatography on 75 g of silica gel, eluting the desired compound with petroleum ether/ethyl acetate 99:1. 0.9 g of dodecahydrohyperforin are obtained, having the following spectroscopical characteristics:

EIMS *m/z* 548 $[M]^+$.

Example 6 - Preparation of acetyloctahydrohyperforin.

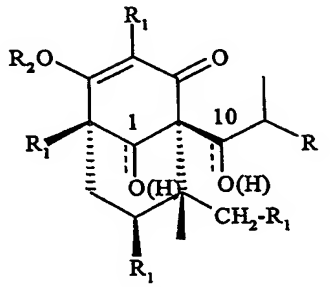
300 mg of acetylhyperforin (M.W.=578; 0.52 mmol) are dissolved in 3 ml of MeOH in a two-necked round-bottom flask, then the catalyst (5% Pd on charcoal) is added. The reaction is monitored by TLC (petroleum ether/EtOAc 95:5 Rfp=0.43; Rfa=0.52). After four hours the reaction is completed. The catalyst is filtered off through a layer of Celite, then methanol is evaporated off.

The reaction product is purified by column chromatography on 30 g of silica gel, eluting with a petroleum ether/ethyl acetate 9:1 mixture. Crystallization from methanol affords 150 mg of the desired compound having the following spectroscopical characteristics:

EIMS *m/z* 586 $[M]^+$.

CLAIMS

1. Hyperforin and adhyperforin derivatives of formula (I)



(I)

in which R is methyl or ethyl, R_2 is hydrogen, a pharmaceutically acceptable inorganic or organic base cation or a straight or branched C_2-C_5 acyl residue, and in which, alternatively:

a) R_1 is 3-methyl-but-1-yl and oxo groups are present at the 1- and 10- positions;

b) R_1 is 3-methyl-2-buten-1-yl and hydroxy groups are present at the 1- and 10- positions;

c) R_1 is 3-methyl-but-1-yl and hydroxy groups are present at the 1- and 10- positions;

for use as medicaments.

2. Derivatives as claimed in claim 1 for the preparation of medicaments for use in the treatment of depression and Alzheimer's disease.

3. Derivatives as claimed in claims 1 or 2 in which R_2 is hydrogen.

4. Derivatives as claimed in claims 1 or 2 in which R_2 is lithium, R_1 is 3-methyl-but-1-yl and oxo groups are present at the 1- and 10- positions.

5. Derivative as claimed in claim 4 in which R is methyl.

6. Derivatives as claimed in claims 1 or 2 in which R_2 is acetyl, R_1 is 3-methyl-but-1-yl and oxo groups are present at the 1- and 10- positions.

7. Derivative as claimed in claim 6 in which R is methyl.

8. A compound selected from:

dodecahydrohyperforin (**Ie**), dodecahydroadhyperforin (**If**), acetyloctahydrohyperforin (Ih) and acetyloctahydroadhyperforin (**Ii**).

9. Pharmaceutical compositions containing the compounds of claim 4.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04100

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C49/733 C07C49/743 C07C69/013 A61K31/122 A61K31/215
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 64388 A (INDENA SPA) 16 December 1999 (1999-12-16) cited in the application claims	1,2
A	WO 99 41220 A (CHATTERJEE SHYAM SUNDER ;SCHAECHTELE CHRISTOPH (DE); SCHWABE WILLM) 19 August 1999 (1999-08-19) cited in the application claims 1,11	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 July 2003	23/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonnevalle, E

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/04100

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